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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/510,001 | 09/30/2004 | Masayuki Amagai | 4439-4025 | 3825 |

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| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/14/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/510,001 | AMAGAI ET AL. | |
| | Examiner | Art Unit | |
| | Phillip Gambel | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment, filed 06/29/2007, has been entered.

Claims 2 and 4 have been canceled.

Claims 1 and 3 have been amended.

Claims 1 and 3 are pending and being acted upon in the instant application.

Again, it is noted that for examination purposes, the claimed recitations of "a remedy" and a preventive agent" are read as compositions or formulations comprising a CD40L antagonist (e.g., see page 9, paragraph 2 of the instant specification).

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 06/29/2007.

The rejections of record can be found in the previous Office Action, mailed 3/29/2007.

3. Upon consideration of applicant's amendment, filed 06/29/2007; the previous rejection under 35 U.S.C. § 112, second paragraph, has been withdrawn.

4. Claims 3 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the reasons of record.

Applicant's arguments, filed 06/29/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant asserts that pemphigus is induced by autoantibodies against desmoglein and that the mouse model, as exemplified in the instant specification, would be the appropriate model for human therapy.

Although not cited on an Information Disclosure Statement,
applicant further relies upon the submission of the Abstracts only of Starzycki, et al. (International Journal of Dermatology 37(3):211-214, 1998), Katzenelson, et al. Dermatologica 181 (1):48-50, 1990) and Tur, et al. (Arch Dermatol. 134(11 ): 1406-1410, 1998) to support the position that it was known that certain people were predisposed to pemphigus and that there were instances where it would be useful to utilize the instant invention to prevent the onset of pemphigus.

Applicant further asserts that the instant invention could be utilize to prevent the reoccurrence of the disease.

It is noted that applicant has not provided direction in the application as-filed to teach the skilled artisan how to make and use the information that certain people were predisposed to pemphigus or to utilize anti-CD40L antibodies the to prevent the reoccurrence of the disease.

Further, applicant has not sufficiently addressed the unpredictability and inconsistency of treating patients with pemphigus, as evidenced by The Merck Manual of Diagnosis and Therapy, Seventeenth Edition (edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999; see pages 829-831) of record and reiterated below.

Also, with respect to animal models, applicant has not sufficiently addressed the following also of record and reiterated below.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human disorders or diseases such as pemphigus targeted by the claimed "preventative agents". With respect to in vivo studies, animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Generally, such diseases are diagnosed only after significant tissue damage has occurred.

The following is reiterated for applicant's convenience.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo experimental observations as well as the clinical experience with targeting various inflammatory conditions with CD40L- specific antibodies accurately reflects the relative ability or efficacy of the claimed "preventative agents" to prevent pemphigus.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.
See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively prevent pemphigus by administering CD40L-specific antibodies / CD40L antagonists. The specification does not teach how to extrapolate data obtained from various in vitro or in vivo observations as well as clinical experience with CD40L-specific antibodies / CD40L antagonists to the development of effective methods of preventing pemphigus in humans broadly encompassed by the claimed invention.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human disorders or diseases such as pemphigus targeted by the claimed "preventative agents". With respect to in vivo studies, animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Generally, such diseases are diagnosed only after significant tissue damage has occurred.

For example, The Merck Manual of Diagnosis and Therapy, Seventeenth Edition (edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999; see pages 829-831) indicates that:
Pemphigus is a serious disease with an inconsistent and unpredictable response to therapy and that the aim of treatment is to stop the eruption of new lesions.
See Treatment on page 829.

Therefore, the treatment of pemphigus is drawn to the treatment of the disease and its associated lesions subsequent to an individual being diagnosed with pemphigus and not as a preventative agent of the disease itself, as recited in the current claims.

There is insufficient guidance and direction as well as objective evidence to provide for preventing pemphigus recited in the instant claims.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to prevent pemphigus with therapeutic agents, undue experimentation would be required to practice the claimed "preventative agents" to prevent pemphigus with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed "preventative agents" and absent working examples providing evidence which is reasonably predictive that the claimed "preventative agents" are effective for preventing pemphigus encompassed by the claimed products.

Applicant's arguments have not been found persuasive.

Again, applicant is invited to amend the claims to avoid the recitation of "a preventive agent".

5. Upon reconsideration of applicant's amended claims, filed 06/29/2007, the previous rejection under 35 U.S.C. 112, first paragraph, written description, with respect to the recitation of "an antagonist that inhibits the interaction between CD40L receptor mediating the contact-dependent helper effector function on the T cell surface and a CD40 receptor on the antigen-presenting cell surface", has been withdrawn.

6. Claims 1 and 3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Black et al. (U.S. Patent No. 6,001,358) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 06/29/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's assertions that the prior art does not disclose that the anti-CD40L antibody is effective in preventing pemphigus, does not provide experimental data and is an incomplete invention,

applicant is reminded that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963). Also, see MPEP 2111.02

Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Further, applicant ignores the claims of Black et al. (U.S. Patent No. 6,001,358). U.S. patents are presumed valid by U.S. courts unless proven otherwise. See 35 U.S.C. 282.

Also, it is noted that proof of efficacy is not required in order for prior art reference to be enabling for purposes of anticipation. See Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc., 81 USPQ2d 1001 (Fed. Cir. 2006).

The following is reiterated for applicant's convenience.

Black et al. teach antagonistic anti-CD40L antibodies, including compositions thereof (e.g., see columns 34-38) as well as their use in the inhibition of CD40L:CD40-mediated interactions, including the treatment of autoimmune and non-autoimmune conditions (e.g., see columns 31-34), including pemphigus (e.g., see column 33, lines 4-5) (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antagonistic anti-CD40L antibodies and therapeutic compositions thereof.

Applicant's arguments have not been found persuasive.

7. Upon consideration of applicant's *amended claims to limit the claimed active agent to anti-CD40L antibodies*, the previous rejection under 35 U.S.C. § 102(b) as being anticipated by Armitage et al. (U.S. Patent No. 6,264,951) has been withdrawn.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
September 5, 2007